HRSA-CDC Task Force: Updating the Vaccine Injury Table (VIT) Following the 2011 IOM Report on Adverse Effects of Vaccines

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Vaccine/Adverse Event Pairs Where No Action or Limited Action was Taken Following Phase 2 Review

Vaccine	Adverse Event	VIT Revision
Influenza	LAIV and asthma exacerbation/reactive airway disease episodes	No – LAIV not approved in affected age group and no evidence of long term sequelae
Influenza	Febrile seizures	No – no evidence of long term sequelae
Influenza	Guillian-Barré syndrome (GBS)	Deferred
Hepatitis A	Anaphylaxis	No – evidence not available
DT, TT, or aP containing	Encephalitis/Encephalopathy	Yes – conditions already listed on Table but QAI will be updated
Injection-Related	Complex Regional Pain Syndrome	No – sufficient evidence not yet available

LAIV and Exacerbation of Reactive Airway Disease Episodes in Children < 5 y/o

- IOM causality conclusion
  - The evidence is inadequate to accept or reject a causal relationship between LAIV and asthma exacerbation or reactive airway disease episodes in children younger than 5 years of age
- HRSA-CDC Phase 2 review
  - Focused on Belshe et al. (2004)*
    - Post hoc analysis of Bergen et al. (2004)†, relative risk for asthma and/or reactive airway disease in the 42 days after LAIV was elevated in children 12-59 months old, but no increased risk in children aged 36-59 months old; no clustering of medical utilization after vaccination
- Phase 2 decision: No VIT revision indicated
- Justification for Phase 2 decision
  - Risk limited to children in an age range (<2 y/o) for which LAIV is not currently licensed
  - No evidence of long-term sequelae

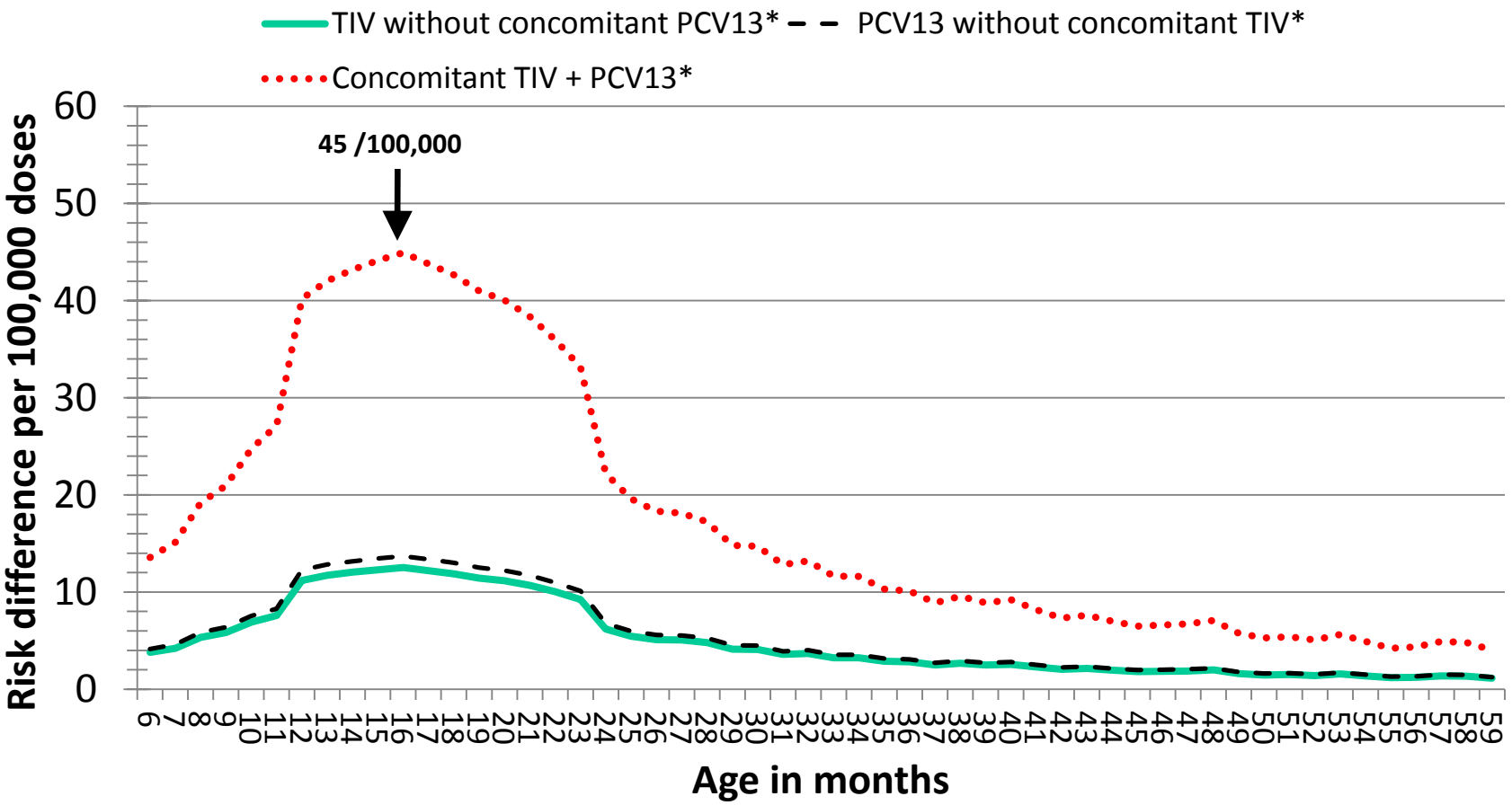
*Belshe et al. Safety, efficacy, and effectiveness of live, attenuated, cold-adapted influenza vaccine in an indicated population aged 5-49 years. Clin Infect Dis. 2004;39:920-7.

†Bergen et al. Safety of cold-adapted live attenuated influenza vaccine in a large cohort of children and adolescents. Pediatr Infect Dis J. 2004;23:138-44.

TIV and Febrile Seizures in Young Children

- IOM Causality Conclusion
  - The evidence is inadequate to accept or reject a causal relationship between influenza vaccine and seizures (note: not febrile seizure specifically)
- HRSA-CDC Phase 2 review
  - Noted that IOM initiated its work prior to the 2010-11 influenza season and therefore did not review data from that season
  - During the 2010-11 influenza season, signals were detected for febrile seizures in VAERS data mining and for seizures in active surveillance in the Vaccine Safety Datalink (VSD) in young children
  - The outcome during the 2010-11 season was specifically febrile seizure in children 6 mo-4 years old
  - Not observed for prior seasonal TIVs
- Phase 2 decision: No VIT revision indicated
- Justification for Phase 2 decision
  - No evidence of long-term sequelae
  - Similar rationale applied for MMR and febrile seizures

Attributable Risk (AR) estimates for febrile seizures following 1st dose TIV, 2010-11^



^Tse A and Lee G for the VSD

*Vaccines may have been received concomitantly with non-TIV, non-PCV13 vaccines

Influenza Vaccine and GBS

- IOM causality conclusion
  - The evidence is inadequate to accept or reject a causal relationship between influenza vaccine and GBS
- Issues for the HRSA-CDC Task Force to consider
  - 1976 swine influenza vaccine was not included in this IOM report because it had been addressed in a previous IOM report (2003); this IOM committee was charged to consider seasonal influenza vaccines
  - IOM initiated its work prior to the H1N1 pandemic and therefore did not include 2009 H1N1 monovalent vaccine (pandemic H1N1) in its evaluation
  - The A/California/07/2009 X-179A (H1N1) strain has been included in seasonal influenza vaccine for 2010-11 and 2011-12
  - 2 studies using Emerging Infections Program (EIP) data, a Vaccine Safety Datalink (VSD) study, a Post-Licensure Rapid Immunization Safety Monitoring (PRISM) study and a study using Medicare data on GBS following H1N1 vaccine have been submitted for publication
  - HHS meta-analysis of GBS following H1N1 vaccine is in progress

Sandhu S. Update on Surveillance for Guillain-Barré Syndrome after Vaccination with Pandemic Influenza A/H1N1 2009-containing Vaccines, 2009–2011. Presentation at VRBPAC, November 16, 2011*

End of Season Results
Influenza A/H1N1 2009 Monovalent Vaccine, 2009–10*

Vaccine Safety System	Chart confirmed GBS Cases (within 42 days)	Study Design	RR
EIP GBS Surveillance	29	Unvaccinated persons	1.57†
		Self-controlled	2.1†
CMS	14	Risk interval (Primary analysis)	1.3
	17	Risk interval (Secondary analysis)	2.8†
VSD	9	Self-controlled	4.4†
		Case-centered	2.0
PRISM	6	Self-controlled	3.3
		Case-centered	3.7
DoD	6	Self-controlled	1.9
VA	2	Historical control	3.95
		Self-controlled	3.86

- High degree of variability in the RR suggests that chance or uncontrolled confounding could contribute to the findings
- An HHS funded meta-analysis is in process.

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* Slides adapted from Presentation by Dr. Claudia Vellozzi at ICPE 2011; † P-value < 0.05

*http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/VaccinesandRelatedBiologicalProductsAdvisoryCommittee/ucm284557.htm

Influenza Vaccine and GBS

- HRSA-CDC Phase 2 review
  - In the unpublished data, the increased risk for GBS following H1N1 inactivated influenza vaccine tended to be relatively small
  - Risk for GBS following H1N1 inactivated influenza vaccine was similar to risk observed for seasonal TIV in some past seasons (when sample sizes were sufficient to detect a small risk), but less than that observed for the 1976 swine influenza vaccine
  - No increased risk for GBS observed for 2009-10 seasonal TIV
  - No increased risk for GBS observed in 2010-11 VSD surveillance or for 2011-12 thus far
  - No VAERS data mining signals for GBS following influenza vaccination in 2010-11 or for 2011-12 thus far
  - FDA analysis of 2010-11 CMS ICD-9 data (automated data, inpatient setting only)*
    - Cohort analysis – relative risk 1.25, statistically significant
    - Risk interval analysis – no statistically significant association
  - No signal for FDA analysis of 2011-12 CMS ICD-9 data (automated data, inpatient setting only)
- Phase 2 decision: Defer action
- Justification for Phase 2 decision
  - Allow completion of the peer review and publication process for the H1N1 vaccine and GBS studies before making a final decision

*Sandhu. Nov 2011 VRPBSC meeting: http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/VaccinesandRelatedBiologicalProductsAdvisoryCommittee/ucm284557.htm

Hepatitis A and Anaphylaxis

- IOM review
  - No studies were identified in the literature for the committee to evaluate the risk of anaphylaxis after the administration of hepatitis A vaccine
- IOM causality conclusion
  - The evidence is inadequate to accept or reject a causal relationship between hepatitis A vaccine and anaphylaxis
- HRSA-CDC Phase 2 review
  - No additional data found on risk of anaphylaxis after the administration of hepatitis A vaccine
- Phase 2 decision: No VIT revision indicated
- Justification for Phase 2 decision
  - Evidence not available

DT, TT or aP containing and Encephalitis and Encephalopathy

- IOM causality conclusion
  - The evidence is inadequate to accept or reject a causal relationship between diphtheria toxoid-, tetanus toxoid-, or acellular pertussis-containing vaccine and encephalitis and encephalopathy
- HRSA-CDC Phase 2 review and justification for Phase 2 decision
  - Previously described during the session on proposed changes to the Qualifications and Aids to Interpretation for DT, TT or aP containing vaccines
- Phase 2 decision
  - Keep encephalitis and encephalopathy on the VIT
  - Update Qualifications and Aids to Interpretation for acute and chronic encephalopathy and for encephalitis

Injection-Related Complex Regional Pain Syndrome (CRPS)

- IOM causality conclusion
  - The evidence is inadequate to accept or reject a causal relationship between the injection of a vaccine and CRPS
- Mechanistic evidence the IOM reviewed was suggestive but not sufficient to make a determination of a causal relationship
- HRSA-CDC Phase 2 review
  - Identified a small number of other published and unpublished case reports (5 total) meeting International Association for the Study of Pain (IASP) criteria for the diagnosis of CRPS
  - Cases exhibited a close temporal association to injection (within 24 hours) making an alternate unrecognized inciting incident unlikely and suggesting the mechanistic evidence supported a causal relationship
- Phase 2 decision: No VIT revision indicated
- Justification for Phase 2 decision
  - Additional mechanistic evidence obtained during the HRSA-CDC review was suggestive but not sufficient to make a determination of a causal relationship

Questions?

Extra slide

Vellozzi C. Monitoring the Safety of Influenza A (H1N1) 2009 Monovalent Vaccines, United States. Presentation at 27th International Conference on Pharmacoepidemiology & Therapeutic Risk Management, August 2011

Summary of Preliminary GBS Results from U.S. 2009-H1N1 Vaccine Safety Surveillance Systems

Vaccine Safety System	GBS cases (42 days after H1N1 vaccination)	Source	Study design	End of Season analysis (95% CI)
EIP GBS Surveillance	29	Chart confirmed	Unvaccinated control Self control	1.57(1.02,2.21) 2.1 (1.2,3.5)
VSD	9	Chart confirmed	Historical control Self control Case-centered	2.44 (0.96,5.42) 4.4(1.3, 14.2) 2.0 (0.5,8.1)
PRISM	25	ICD-9	Historical control Self control	0.66(0.38,1.16) 1.47 (0.6,3.24)
CMS	14	Chart confirmed	self control	1.3 (0.5, 3.1)
DoD	8	ICD-9	Historical control	1.38
VA	3	ICD-9	Historic control Self control	1.76(0.70, 3.62)* 1.29 (0.24, 7.05)

*standardized incidence ratio

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http://www.pharmacoepi.org/meetings/27thconf/presentations/Monitoring%20the%20Safety%20of%20Influenza%20A%20(H1N1)%202009%20Monovalent%20Vaccines,%20United%20States.pdf